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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/005,747	Applicant(s) Slavin
	Examiner G.R. Ewoldt, Ph.D.	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *8/14/02, 8/20/02, and 1/29/03*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *20-38* is/are pending in the application.

4a) Of the above, claim(s) *22-26 and 35-38* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20, 21, and 27-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of Group I, Claims 20, 21, and 27-34, in Paper No. 8, filed 8/14/02, without traverse, is acknowledged. Upon further consideration, Groups I-III are hereby rejoined and considered three species of a single invention. Applicant's election of Group I will be considered an election of the first species of the claimed method.

2. Claims 22-26 and 35-38 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected species.

3. Applicant is advised that a handwritten change has been found at page 50, line 6 of the specification. Accordingly, this application is not a Continuation of parent application 08/735,496, but rather a Continuation-in-Part. A new declaration reflecting said change is required.

4. The first line of the specification must be amended to disclose all of the updated priority data.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 20, 21, and 27-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) The recitation of "HLA-compatible, allogeneic peripheral blood lymphocytes," is vague and indefinite as the term is not defined in the specification. While the disclosure, at page 11, includes some discussion of the types of stem cells that might be acceptable for transplantation, the "HLA-compatible" cells of the claims are not actually defined. Note that the additional limitations regarding the "HLA-compatible" cells set forth in Claims 32-34 cannot serve to define the cells because the limitations do not disclosed which cells are encompassed, and which cells are not, in the absence of the limitations.

B) The recitation of "administering to said patient HLA-compatible, allogeneic peripheral blood lymphocytes in a regimen that causes a clinically mild graft-versus-host response," is vague and indefinite as the metes and bounds of said response are not defined in the specification. At page 8 of the specification it is disclosed, "As used herein, the term "graft-versus-host

response" includes but is not limited to the classic clinical symptoms of graft-versus host disease (GVHD), known to those having ordinary skill in the art. The term "graft-versus-host response" also includes molecular or cellular responses that correlate with the clinical symptoms of GVHD or with the impending onset of the clinical symptoms of GVHD." Note that the specification specifically discloses that the term is not limited to GVHD, but is also intended to include other types of "responses". The specification fails, however, to adequately define the additional "molecular or cellular responses that correlate with the clinical symptoms of GVHD," encompassed by the method of the claims.

C) The recitation of "wherein said administering is after patient is partially hematopoiesis recovered but is not fully immune reconstituted," is vague and indefinite as the metes and bounds of the time frame encompassed by this limitation is not defined in the specification. Also note that "patient" would properly be "said patient".

D) In Claim 31, "where in" would properly be "wherein".

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 20, 21, 27, 28, 30, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable Slavin (1992) in view of Johnson, et al. (1993) and Slavin et al. (1990).

Slavin teaches the basic concept of the invention of the instant claims, i.e., autologous stem cell transplantation after tumor debulking followed by an infusion of allogeneic donor lymphocytes intended to achieve a graft-versus-leukemia (GVL) effect, which may include graft-versus-host disease, as a treatment for a hematologic malignant disease e.g., leukemia (see particularly page 6, column 2).

The reference teaching differs from the claimed invention only in that it does not teach some of the specific limitations of the claims, such as the use of HLA-compatible donor lymphocytes, the induction of a mild graft-versus-host response, the timing of therapy, i.e., the administration of donor lymphocytes after partial hematopoietic recovery but before full

recovery, the source of said lymphocytes (bone marrow or peripheral circulation), or the type of cancer (leukemia or lymphoma).

Johnson et al. teaches that in the absence of GVHD, the rate of leukemia relapse is greater because it is donor T cells (lymphocytes that are responsible for the GVL effect) that induce the GVL effect. The reference discusses the possibility of inducing GVL while minimizing GVHD and teaches that insignificant or a mild GVH is acceptable as part of the GVL effect (see particularly the last sentence of the Abstract and page 332, column 1 last paragraph - column 2 first paragraph).

Slavin et al. teaches the administration of donor lymphocytes after partial hematopoietic recovery but before full recovery and the use of HLA-compatible lymphocytes (see entire Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of autologous stem cell transplantation after tumor debulking followed by an infusion of allogeneic donor lymphocytes intended to achieve a GVL effect which may include graft-versus-host disease as a treatment for a hematologic malignant disease, e.g. leukemia, as taught by Slavin. One of ordinary skill in the art at the time the invention was made would have been motivated to allow a certain degree of GVHD, as taught by Johnson et al., because this would have been a known minor tradeoff for effective GVL, i.e., the T cells that induce the GVL also induce some GVHD. One of ordinary skill in the art at the time the invention was made would have been motivated to administer the donor lymphocytes after partial hematopoietic recovery but before full recovery and the use of HLA-compatible lymphocytes, as taught by Slavin et al., because this timing of administration would seem to be the most logical possibility. Administering the donor lymphocytes with bone marrow transplantation was well known to induce GVHD while administering the donor lymphocytes long after transplantation would allow for the residual disease to reestablish itself. Note that the "monitoring" requirement of the claims comprises a routine part of all oncological treatments and is therefore obvious. Note that the Claims 27 and 28 are included in the rejection because bone marrow and peripheral circulation are the most obvious sources of human stem cells. Claims 32-34 are included in the rejection because the claims recite the types of donor cells that would most obviously be "HLA-compatible", i.e., fully HLA matched, haploidentical, and HLA-single mismatched. It is well known in the transplantation

arts to seek the most compatible donors for successful transplantation, thus the recitation of such would be obvious.

9. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Slavin (1992) in view of Johnson, et al. (1993) and Slavin et al. (1990), as applied to Claims 20, 21, 27, 28, 30, and 32-34 above, and in further view of Straus et al. (1991).

Slavin (1992), Johnson, et al. (1993) and Slavin et al. (1990) have been discussed above.

The combined reference teachings differ from the claimed method in that they do not teach a method of treating lymphoma.

Straus et al. teaches the well known fact that treatments for leukemia and lymphoma are closely related and often interchangeable (see Abstract, Purpose).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of autologous stem cell transplantation after tumor debulking followed by an infusion of allogeneic donor lymphocytes intended to achieve a GVL effect which may include graft-versus-host disease as a treatment for a hematologic malignant disease, as taught by Slavin. One of ordinary skill in the art at the time the invention was made would have been motivated to allow a certain degree of GVHD, as taught by Johnson et al., because this would have been a known minor tradeoff for effective GVL. One of ordinary skill in the art at the time the invention was made would have been motivated to administer the donor lymphocytes after partial hematopoietic recovery but before full recovery and the use of HLA-compatible lymphocytes, as taught by Slavin et al., because this timing of administration would seem to be the most logical possibility. Administering the donor lymphocytes with bone marrow transplantation was well known to induce GVHD while administering the donor lymphocytes long after transplantation would allow for the residual disease to reestablish itself. One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method as a treatment for lymphoma because treatments for leukemia and lymphoma are closely related and often interchangeable, as taught by Straus et al.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts are such that no methods are currently available for obtaining one's own fetal tissue as would be encompassed by the instant invention as claimed.

The claimed method comprises a method of autologous, i.e., one's own stem cell transplantation. The claim recites the use of stem cell's obtained from a fetus or cord blood. Thus, the claim requires that one obtain one's own fetal tissue or cord blood. Note the differentiation, i.e., the recitation of both fetal tissue and cord blood. Clearly they are different compositions as demonstrated by the recitation of both. Accordingly, cord blood is not fetal tissue. While it is conceivable that one's cord blood could be retained from birth, this requirement is not disclosed in the specification, and it was not a common practice in 1994. The only way one might obtain one's own fetal tissue would be to clone oneself, abort the clone, and obtain the tissue. This procedure, i.e., human cloning, was not enabled in 1994. Accordingly, the method of the claim must be considered highly unpredictable. Given said unpredictability, the method of the instant claim must be considered to require undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, i.e., the specification discloses no cloned humans, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

13. Claims 20 and 27-34 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 7-14 of prior U.S. Patent No. 5,928,639. This is a double patenting rejection.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claim 21 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,928,639. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim recites the limitation that the treatment causes a clinically significant graft-versus-malignant cell response. It would be clear to one of ordinary skill in the art that the point of a treatment would be a clinically significant response. Accordingly, the limitation does not render the claim patentably distinct.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 7:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 at (703) 305-3014. The CM1 Fax Center telephone numbers are 703-872-9306 (before final) and 703-872-9307 (after final).

G.R. Ewoldt, Ph.D.
Patent Examiner
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June 24, 2003

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